

Original Research Article

Title: Chronic Kidney Disease among Ghanaian HIV Individuals on HAART in the Ho Municipality: A single-center descriptive cross-sectional study

Abstract

Background: Chronic kidney disease (CKD) remains one of the complications of HIV infection among individuals on antiretroviral medication. This study aimed to determine the prevalence of CKD among Ghanaians with HIV on antiretroviral medications at the Ho Municipal Hospital.

Materials and Methods: A hospital-based cross-sectional study involving 170 previously diagnosed HIV-infected patients on HAART treatment aged between 24-78 years attending ART clinic at the Ho Municipal Hospital were purposively recruited from February to May 2017. Using patients' folders, data on patient age, gender, type of medication(s) and duration on HAART medication were obtained. Patient's blood sample was taken for the estimation of CD4 count and serum creatinine concentration. . Estimated glomerular filtration rate (eGFR) was calculated from serum creatinine using the four-Variable Modification of Diet in Renal Disease (4v-MDRD), and Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equations.

Results: The prevalence of CKD was estimated at 17.1% and 18.8% using the 4v-MDRD and the CKD-EPI equations respectively. Females recorded a higher prevalence (20.0% and 22.14%) compared to their male counterparts (3.33 % and 3.33%) using the 4v-MDRD and CKD-EPI equations respectively. Low immunological recovery (CD4 cell count <500 cell/mm³) and longer duration on HAART (7-9 years) accounted for higher CKD prevalence.

Conclusion: In these patients receiving HAART treatment at the Ho Municipal Hospital, a high burden of CKD was observed among the female group. HAART

regimens involving Nevirapine and Tenofovir had the highest association with CKD among the participants.

Keywords: Human immunodeficiency Virus, Chronic Kidney Disease, Estimated Glomerular Filtration Rate, HAART toxicity

Introduction

Highly Active Antiretroviral Therapy (HAART) has changed the characteristic history of HIV-infection profoundly and transformed the disease into a chronic condition since its introduction decades ago (1). The advent of HAART has been linked to a significant reduction in morbidity and mortality from HIV/AIDS (2). The therapeutic target is to suppress viral load and facilitate the resuscitation of the immune system as well as protect the individual from the development of AIDS and death (3). However, comorbid conditions have been associated with HAART-treated patients, often frustrating the clinical management of these immune compromised individuals (4). Renal disease, for instance, is progressively prevalent in individuals with HIV and is a major cause of death in this population (5). Renal damage due to antiretroviral drug toxicity can bring about a variety of toxic drug effects which may manifest as acute renal failure, tubular necrosis, kidney stones, or chronic renal disease (4). Hence, renal dysfunction may be a typical finding in patients infected with HIV, and requires increased surveillance and adjustment of dosages of HIV medications (6). Despite its clinical importance among HIV individuals on antiretroviral therapy, very few studies have been conducted to ascertain the burden of renal toxicity in the Ghanaian

population. The prevalence of CKD among Ghanaians living with HIV infection is reported to range from 3.7% in the Ashanti Region to 12.6% in the Upper-East Region (2, 4, 7). However, there is very little information in the literature about the burden among HIV registrants attending antiretroviral therapy (ART) clinics in the Volta region of Ghana. To fill this knowledge gap, the present study sought to determine the prevalence of chronic kidney disease among HIV cohorts at the Ho Municipal Hospital in Ghana. Knowledge on the renal capacity status of such people could enhance management approaches and guide future prescribing practice (4, 8) .

Materials and Methods

The Study Site, Design and Population

A single-center hospital-based, descriptive cross sectional study was conducted between February and May 2017 at the ART clinic and the Medical Laboratory of the Ho Municipal Hospital in the Volta region, Ghana. One hundred and seventy (170) previously diagnosed HIV-infected patients attending ART management clinic were conveniently and purposively recruited for this study. The study population were of consent age (24– 78 years) and were all living in the Ho municipality.

Sample Size Determination

Using the average monthly attendance of HIV-infected patients at the ART Clinic (55) for two previous months (December 2016 and January 2017), a total study population of

220 was generated for the four months study duration. Using the Raosoft online sample size calculator (<http://www.raosoft.com/samplesize.html>), the recommended minimum sample of 141 participants was calculated at 95% confidence level, 5% margin of error, and a response distribution of 50%.

Laboratory Analysis

All laboratory assays were carried out at the Ho Municipal Hospital laboratory. Venous blood samples was drawn from the antecubital vein of which three (3) milliliters was dispensed into a vacutainer® serum separator tube and one (1) milliliters was dispensed into EDTA anticoagulant tube using the closed vacutainer system. CD4 lymphocyte count by flow cytometry was performed using 50uL of non-haemolyzed whole blood with the BD FACSCount™ system according to the manufacturer method (Becton Dickenson and Company, California, and USA). The sample in the serum separator was centrifuged at 2500 revolutions per minute (rpm) for 5 minutes at room temperature to obtain the serum used for the assay of creatinine. Creatinine assay was carried out using predetermined methods by the reagent manufacturer (ELITech Clinical Systems, SAS, Zone Indusrielle-61500 SEES, France), on the Random Access Fully Automated Vitalab Selectra Junior Chemistry analyzer (Vital Scientific, BV Kanaalweg 24, The Netherlands).

Glomerular Filtration Rate Estimation

Renal function among study participants were estimated using the following CKD equations:

I. Four Variable Modification of Diet in Renal Disease (4v-MDRD)

$$a. \text{Males} = 186 \times \text{Scr}^{-1.154} \times \text{Age}^{-0.203} \times (1.210)$$

$$b. \text{Females} = 186 \times \text{Scr}^{-1.154} \times \text{Age}^{-0.203} \times (1.210) \times 0.742$$

Where Scr= Serum creatinine concentration

II. Chronic Kidney Disease Epidemiology collaboration (CKD-EPI)

$$a. \text{Females } (\leq 62\mu\text{mol/L}) \text{ eGFR} = 166 \times \left(\frac{\text{serum creatinine}}{0.7} \right)^{-0.329} \times (0.993)^{\text{Age}}$$

$$b. \text{Females } (> 62\mu\text{mol/L}) \text{ eGFR} = 166 \times \left(\frac{\text{serum creatinine}}{0.7} \right)^{-1.209} \times (0.993)^{\text{Age}}$$

$$c. \text{Males } (\leq 80\mu\text{mol/L}) \text{ eGFR} = 163 \times \left(\frac{\text{serum creatinine}}{0.9} \right)^{-0.411} \times (0.993)^{\text{Age}}$$

$$d. \text{Males } (> 80\mu\text{mol/L}) \text{ eGFR} = 163 \times \left(\frac{\text{serum creatinine}}{0.9} \right)^{-1.209} \times (0.993)^{\text{Age}}$$

Chronic Kidney Disease Definition

The eGFR results from the various renal function equations were used to stratify the study population into five categories corresponding to the five stages of CKD in the

K/DOQI CKD classification. Chronic kidney disease was classified as eGFR < 60 mL/min/1.73 m² (stages 3, 4 and 5; See Table 3)(9).

Statistical Analysis

Normality of all continuous variables were tested. Continuous parametric variables were expressed as their mean $\pm$ standard deviation, continuous nonparametric variables were expressed as median (minimum and maximum), whereas categorical variables were expressed as frequency and proportion. Gender variation in the prevalence of chronic kidney disease was tested by Fishers exact test. IBM Statistical Package for the Social Sciences version 22.00 was used for data analysis (SPSS Inc, Chicago, USA; www.spss.com).

Ethical Consideration

Informed consent was obtained from all participants after the study procedure was clearly explained to them in a language they understood (either English or Ewe). Approval for the study was obtained from the Ho Municipal Hospital. Ethical Clearance for the study was granted by the Ethical Review Committee of the School of Allied Health Sciences of the University of Health and Allied Sciences, Ho (**UHAS-SAHS-ERSC:019A/2017**). The research was anonymous and non-linked and no patient name or identity was used during analysis of data.

Results

Out of the 170 participants that were recruited into this study, 140(82.4%) were females and thirty 30(17.6%) were males. Among the study participants who were put on medication, 68(40.0%) were on TDF/3TC/EFV 68(40.0%), the most common ART regimen, followed by TDF/3TC/NVP 46(27.06%), AZT/3TC/EFV 39(22.94%) and least being AZT/3TC/NVP 17(10.00%). All the combination therapy administered had Lamivudine (3TC) as part of the regimen 170 (100%). Tenofovir (TDF) was found in 67.06% of the regimen, whereas Effavirenz (EFV) was found in 62.94% of the combination therapy (See Table 1).

Table 1: Demographic and antiretroviral selection of HIV-infected patients in Ho

Parameter	Frequency	Percentage
Total	170	100
Gender		
Female	140	82.35
Male	30	17.65
ARV Combination Therapy		
TDF/3TC/EFV	68	40.00
TDF/3TC/NVP	46	27.06
AZT/3TC/EFV	39	22.94

AZT/3TC/NVP	17	10.00
ARV Single Component		
3TC	170	100
TDF	114	67.06
EFV	107	62.94
NVP	63	37.06
AZT	56	32.94

Data is presented as frequency and percentage. 3TC-Lamivudine, TDF-Tenofovir, EFV-Effavirenz, NVP- Nevirapine, and AZT- Zidovudine,

The average age of the study participants was 44.42 ± 11.603 . The duration on HAART ranged from a minimum of 1 year to 9 years maximum. The median CD4 count among the participants was $526.50 \mu\text{L}$ ranging from a minimum of $83 \mu\text{L}$ to $1682 \mu\text{L}$. The average creatinine concentration was 91.05 ± 32.82 among the female patients and 94.99 ± 20.60 among the males. Using the Chronic Kidney Disease Epidemiology Collaboration equation, the mean estimated glomerular filtration rate was 87.74 ± 28.60 (mL/min/1.73 m²) and 89.15 ± 34.39 (mL/min/1.73 m²) when the 4v-MDRD: Four Variable Modification of Diet in Renal Disease equation was used (See Table 2).

Table 2: Demographic and biochemical characteristics of HIV-infected patients on HAART stratified by gender

Parameter	Total (170)	Female (140)	Male (30)
Age	44.42±11.603	43.42±11.76	49.07±9.72
Duration	2.00(1-9)	2.00(1-8)	3.00(1-9)
CD4	526.50(83-1682)	535.50(112-1682)	458.50(83-1128)
Creatinine	91.74±31.00	91.05±32.82	94.99±20.60
CKD-EPI	87.74±28.60	85.94±29.41	96.15±23.06
4V-MDRD	89.15±34.39	86.67±34.93	100.68±29.64

Data is presented as mean $\pm$ standard deviation or median with minimum and maximum. CKD-EPI: Chronic Kidney Disease Epidemiology collaboration, 4v-MDRD: Four Variable Modification of Diet in Renal Disease

Using the 4v-MDRD equation in the estimation of glomerular filtration rate, 47.06% of the respondents were classified as stage 1 CKD, 35.88% were classified as stage 2 and 17.06% were classified as stage 3 CKD. No patient presented with stage 4 and stage 5 CKD. The prevalence of CKD was estimated as 17.06% among the study population.

Using the CKD-EPI equation 17.65% and 1.18% presented with stage 3 and 4 CKD respectively. The prevalence of CKD according to the CKD-EPI was therefore 18.82% among the study population (See Table 3).

Table 3: Chronic kidney diseases among patients on HAART in the Ho Municipality staged with 4V-MDRD and CKD-EPI equations

Parameter	4v-MDRD	CKD-EPI
Stage 1 (≥ 90 mL/min/1.73 m ²)	80(47.06)	86(50.59)
Stage 2 (60 To 89 mL/min/1.73 m ²)	61(35.88)	52(30.59)
Stage 3 (30 To 59 mL/min/1.73 m ²)	29(17.06)	30(17.65)
Stage 4 (15 To 29 mL/min/1.73 m ²)	0.0(0.00)	2(1.18)
Stage 5 (<15 mL/min/1.73 m ²)	0(0.00)	0.0(0.00)
CKD(Stage 3+4+5)	29(17.06)	32(18.82)

Data is presented as figure with percentage in parenthesis: CKD: Chronic Kidney Disease, CKD-EPI: Chronic Kidney Disease Epidemiology collaboration, 4v-MDRD: Four Variable Modification of Diet in Renal Disease.

Using the 4v-MDRD equation, the prevalence of CKD was higher among the female participants 28(20.00%), compared to their male counterparts 1(3.33%) $p=0.0305$. When CKD was staged using CKD-EPI equation, 20.71% and 1.43% of the female participants presented with stage 3 and stage 4 CKD respectively. Among the male population, 3.33% presented with stage 3 CKD. The prevalence of CKD was higher among the females 22.14%, than the males 3.33% ($p=0.0183$) (See Table 4).

Table 4: Chronic kidney diseases staged with 4V-MDRD and CKD-EPI equations stratified by gender

Parameter	4V-MDRD		CKD-EPI	
	Female(140)	Male(30)	Female(140)	Male(30)
Stage 1(≥ 90)	61(43.57)	19(63.33)	67(47.86)	19(63.33)
Stage 2(60 To 89)	51(36.43)	10(33.33)	42(30.00)	10(33.33)
Stage 3 (30 To 59)	28(20.00)	1(3.33)	29(20.71)	1(3.33)
Stage 4(15 To 29)	0(0.00)	0(0.00)	2(1.43)	0(0.00)
Stage 5(<15)	0(0.00)	0(0.00)	0(0.00)	0(0.00)
CKD (Stage 3+4+5)	28(20.00)	1(3.33)	31(22.14)	1(3.33)

Data is presented as figure with percentage in parenthesis: CKD: Chronic Kidney Disease, CKD-EPI: Chronic Kidney Disease Epidemiology collaboration, 4v-MDRD: Four Variable Modification of Diet in Renal Disease

Irrespective of the predictive equation used, CKD was found to be higher among patients with CD4 count of 200 to 499 (cell/mm³). Among the HAART combination therapy, patients on TDF/3TC/NVP regimen presented with the highest prevalence of CKD, followed by those on TDF/3TC/EFV regimen. As seen in Table 5, NVP was the drug with the highest CKD occurrence, followed by TDF (See Table 5).

In general, percentage CKD was observed to increase with increasing duration on HAART. Using the CKD-EPI equation, 17.12%, 19.23% and 42.86% of the CKD cases were observed for patients who had been on HAART for the period 1-3 years, 4-6 years and 7-9 years respectively. Staging CKD by the 4v-MDRD equation, 15.32%, 19.23% and 28.57% of the CKD cases were recorded among patients who have been on HAART for the period 1-3 years, 4-6 year and 7-9 years respectively (See Figure 1).

Table 5: Chronic kidney disease stratified by CD4 status, regimen type and component drug among HIV-infected patients

Parameter	4v-MDRD	CKD-EPI	Rank
CD4			
200-499	15(23.81)	17(26.98)	1 st
<200	13(13.98)	14(15.05)	2 nd
≥500	1(7.14)	1(7.14)	3 rd
ARV Combination			
TDF/3TC/NVP	12(26.09)	13(28.26)	1 st
TDF/3TC/EFV	10(14.71)	12(17.65)	2 nd
AZT/3TC/EFV	5(12.82)	5(12.82)	3 rd
AZT/3TC/NVP	2(11.76)	2(11.76)	4 th
Drugs			
NVP	14(22.22)	15(23.81)	1 st

TDF	22(19.30)	25(21.93)	2 nd
3TC	29(17.06)	32(18.82)	3 rd
EFV	15(14.02)	17(15.89)	4 th
AZT	7(12.50)	7(12.50)	5 th

Data is presented as figure with corresponding percentage in parenthesis and rank. CKD-EPI: Chronic Kidney Disease Epidemiology collaboration, 4v-MDRD: Four Variable Modification of Diet in Renal Disease

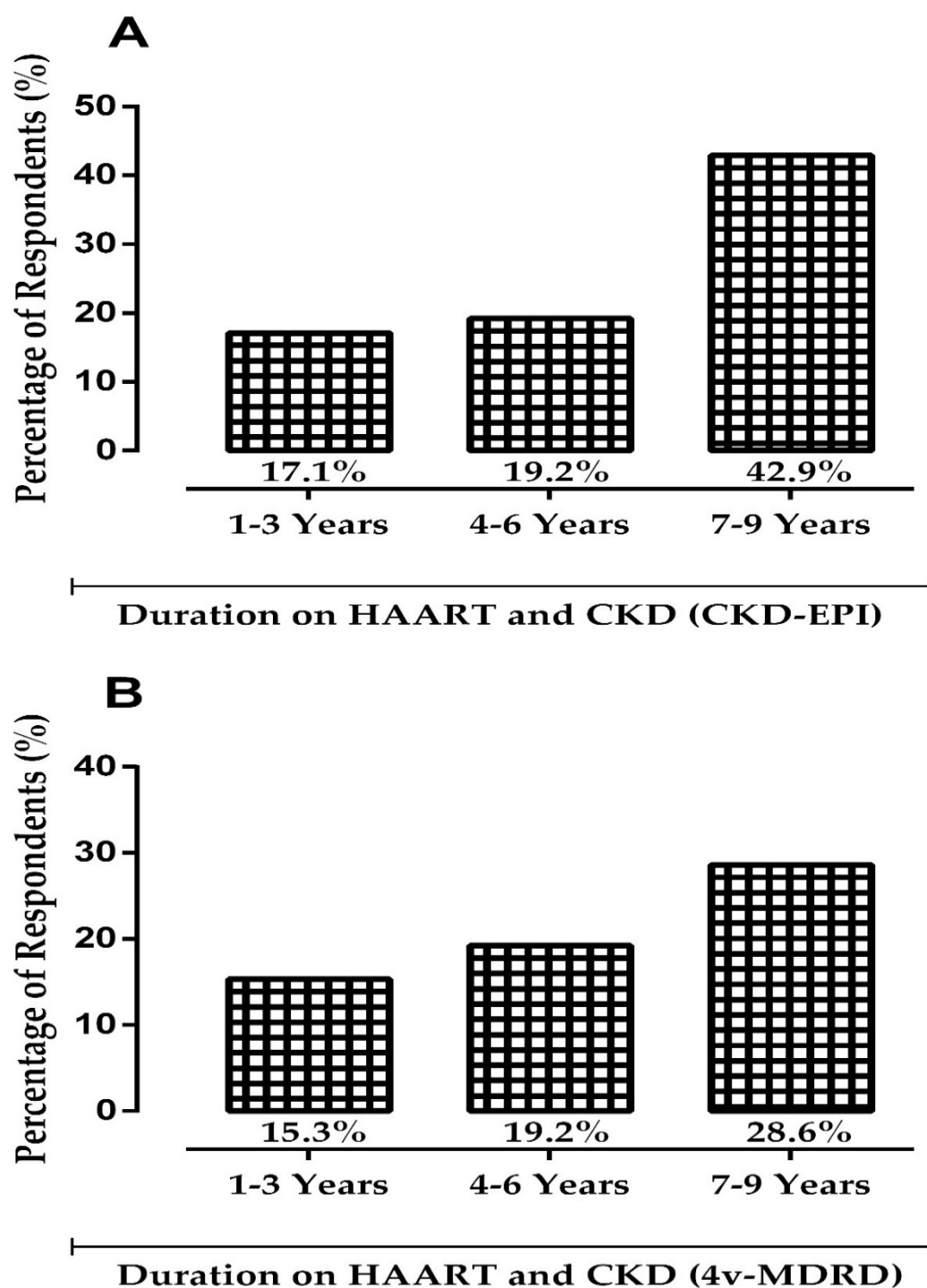


Figure 1 : Duration on HAART and chronic kidney disease according to CKD-EPI and 4V-MDRD

Discussion

Chronic kidney disease (CKD) poses great danger to patients on HAART which could lead to a loss of optimum kidney function, kidney failure, and the development of cardiovascular disease (10). This hospital-based descriptive study sought to determine the prevalence of CKD among HIV registrants on HAART at the ART Clinic of the Ho Municipal Hospital. The prevalence of CKD among the study population was estimated at 17.06% and 18.82% using the 4v-MDRD and CKD-EPI definition criteria respectively (Table 3). Nephrotoxicity associated with HAART treatment remains prevalent among Ghanaian HIV populations, and this has been documented in recent studies. Obirikorang and colleagues reported a prevalence of 9.9% and 3.7% using the 4v-MDRD and CKD-EPI equations respectively in a study conducted at a Sexually Transmitted Infections (STI) Clinic in Kumasi (4). In Bolgatanga, Owiredo *et al.*, (2) recorded a prevalence of 12.6% using both the 4v-MDRD and CKD-EPI equations in a study undertaken at the ART Clinic of the Regional Hospital. HAART related renal insufficiency in the HIV populations is not only limited to the Ghanaian setting. In other jurisdictions, higher CKD burdens have been recorded in Nigeria and Burundi with estimated prevalence of 47.6% and 45.7% among HIV patients respectively (11, 12). Among factors postulated to contribute to the discordant findings in the burden of CKD in HIV populations across various geographical boundaries include differences in

population characteristics including demographic profiles of participants and analytical methods, study design, severity of the disease, type of criteria used for the definition of CKD as well as access to medical care (7, 13).

In the present study, the prevalence of CKD was found to be significantly higher in women than men irrespective of the CKD equation used among the study population (Table 4). Female participants recorded a prevalence of 20.00% CKD compared to the 3.33 % observed among their male counterparts using the 4v-MDRD, whereas using the CKD-EPI equations, the females recorded a percentage CKD of 22.14% in comparison to the 3.33% reported among the males. Our observation is in tandem with that reported by Owiredo *et al.*, (2) where femininity accounted for higher CKD scores. In a review of nephrotoxicity due to HAART therapy in HIV infected individuals, Kalyesubula and Perazella (14) found that, the female gender is associated with renal impairment among other risk variables. The higher CKD prevalence among females observed in this study could be linked in part to the greater proportion of women than men affected by HIV infection in the Ghanaian and African society (2, 4, 15). Factors such as, the better health seeking attitude of women and the higher probability of disease detection and diagnosis among women than men have been suggested to be attributable causes of the disparity in prevalence rates among males and females (11).

Though the management of HIV infected persons with antiretroviral medications has led to some tremendous revolution in their well-being, the treatment regimens have

been associated with organ toxicities, including those affecting the kidney (16). In the present study, among the HAART combination therapies the participants were being managed with, TDF/3TC/NVP regimen presented with the highest CKD prevalence, followed by those on TDF/3TC/EFV regimen. Nevirapine was the drug with the highest CKD occurrence, followed by Tenofovir irrespective of the CKD equations used (Table 5). Consistent with our findings, Nevirapine and Tenofovir medications or their combinations was associated with a greater proportion of the HIV population presenting with CKD in a study reported by Owiredu *et al.*, (2). Tenofovir regimens are said to be more likely to increase CKD in HIV patients than non-Tenofovir-based combinations (17). The precise mechanism by which antiretroviral drugs inflict short and/or long term injury to the kidney is yet to be fully delineated, however, Kalyesubula and Perazella (14) posited that acute tubular necrosis, acute interstitial nephritis, crystal nephropathy, as well as renal tubular disorders are all pathways implicated directly affecting renal function or indirectly via drug interactions.

Immune suppression reflecting low CD4 count and antiretroviral treatment duration have been shown to be independent risk factors for CKD in studies undertaken previously in various HIV populations (10, 18-20). In the current study, irrespective of the CKD equations used, the proportion of participants with CKD was found to be higher among participants with CD4 count less than 500 cells/mm³ (37.79% and 42.03%) compared to those with higher immune recovery (CD4 count more than 500 cells/mm³)

(7.14% and 7.14%) (Table 5). In a lowered immune environment, HIV could cause direct injury to the kidneys manifesting as HIV associated nephropathy (HIVAN) in affected patients (17).

Chronic kidney disease prevalence among participants was observed to increase with increasing duration on HAART irrespective of the CKD equations used (Figure 1). The proposed mechanism of the long-term toxicity of antiretroviral usage particularly Tenofovir induced nephrotoxicity, may be due to increased drug accumulation within the proximal renal tubules, leading to mitochondrial injury and depletion (21).

Conclusion

In these patients receiving HAART treatment at the Ho Municipal Hospital, a high burden of CKD was observed among the female group. HAART regimens involving Tenofovir and Nevirapine had the highest prevalence of CKD among the participants. Type of HAART medication and longer duration on HAART as well as lowered immune recovery could be associated with increased renal toxicity.

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